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A Transdermal Glucagon Patch for Severe Hypoglycemia

Image courtesy of Zosano Pharma

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Summary

- The ZP-Glucagon patch uses novel microneedle technology to deliver glucagon through the skin to people who are experiencing severe hypoglycemia (very low blood sugar).
- There is very limited evidence, from one small study, comparing the ZP-Glucagon patch with glucagon injected intramuscularly.
- The evidence suggests that the correction of blood sugar levels is comparable between the ZP-Glucagon patch and the glucagon injected intramuscularly when tested in a controlled setting.
- The ZP-Glucagon patch is not yet commercially available and the anticipated cost is unknown.
- In an emergency situation, the ZP-Glucagon patch may be a more user-friendly option than injecting glucagon.

Issue

Hypoglycemia occurs when a person's blood glucose (blood sugar) level is too low; it is a common problem in people living with diabetes who are on insulin or insulin secretagogues (drugs that increase insulin secretion by the pancreas).[1] Although the precise thresholds for hypoglycemia and severe hypoglycemia based on blood glucose levels continue to be debated, the severity of hypoglycemia is generally categorized by the clinical symptoms and the type of intervention required.[2,3] Common symptoms of mild or moderate hypoglycemia include difficulty concentrating, trembling, palpitations, sweating, anxiety, confusion, and vision changes.[1] These are typically resolved with the administration of carbohydrates (for example, glucose tablets, juice, or honey).[1]

In severe hypoglycemia, the assistance of another person is required as the patient may experience a loss of consciousness, enter a coma, or have a seizure.[1] Severe hypoglycemia is associated with both short-term risks (for example, when driving or operating machinery) and long-term complications (for example, potential intellectual impairment).[1,2]

Glucagon is the main hormone produced by the body in response to low blood glucose levels.[4,5] It acts on the liver to release glucose into the blood to restore sugar levels to normal.[4,5] Commercially available exogenous (external) glucagon is identical to human glucagon and is used to treat people with severe hypoglycemia who have lost consciousness.[6] Commercial glucagon is supplied as a dry powder and must be mixed with diluent immediately before use and injected intramuscularly or subcutaneously.[6]

An alternative to mixing and injecting glucagon, a microneedle skin patch, is in development. This may be more user friendly in cases of glycemic emergencies.

The Technology

Microneedle technology as a method of transdermal (through the skin) drug delivery has received a great deal of attention in recent years.[7-10] Microneedles consist of micron-scale projections that are considered to be minimally invasive, yet are capable of bypassing the outermost layer of the skin (stratum corneum) without disrupting nerves and blood

vessels, thereby inducing no pain or bleeding when applied.[7,10] The microchannels that result from the projections form an unobstructed transport pathway big enough for large molecules such as proteins and peptides to pass through.[7]

The ZP-Glucagon patch (Zosano Pharma, Fremont, California) is a coin-sized patch that, when applied to the skin using a reusable applicator, delivers glucagon through the skin to ultimately be absorbed into the blood.

Zosano Pharma's proprietary ZP-patch system (which can be used for delivery of various drugs), consists of a 3 cm^2 array of titanium microneedles in the centre of an adhesive patch contained within a retainer ring.[11,12] The microneedles are dry-coated with the drug or compound to be administered (in this case, glucagon). The retainer ring is attached to the bottom of the applicator, which in turn, is activated through spring force. The applicator is positioned on the arm and depressed, causing the adhesive to break away from the retainer ring and the patch to be applied to the skin site.[11] The patch remains applied for 30 minutes after which time it is removed and discarded.[13]

When the patch is applied, the microneedles physically break the outermost layer of skin, and penetrate the epidermis layer below where the dry drug coating is dissolved in the surrounding interstitial fluid.[11] The outer layer of skin provides protection against external microbial pathogens, chemicals, and dehydration, and is also the principal barrier to drugs intended for transdermal delivery.[7] This method of delivery results in rapid dissolution and absorption of administered drugs or compounds through the capillary bed, reaching the desired therapeutic levels in the blood within 20 minutes.[12]

Availability

The ZP-Glucagon patch is not yet commercially available in Canada or elsewhere. According to the company's website (at the time of publication) the ZP-Glucagon patch is in phase II clinical development.[14]

Cost

The anticipated cost of the ZP-Glucagon patch is yet unknown.

Who Might Benefit?

Individuals with type 1 diabetes and type 2 diabetes who are at increased risk of drug- or insulin-induced hypoglycemia, especially those who are attempting intensive control to achieve strict glycemic targets.[15]

Severe hypoglycemia is less frequent in early diabetes because of the body's defenses, which release glucagon and adrenalin to limit large falls in blood glucose.[2] However, as diabetes progresses, the body's ability to release glucagon is impaired and counter-regulatory responses are activated at lower blood glucose levels — which further increase the risk of severe hypoglycemia.[2] As a result, it is important that people with diabetes who use insulin or insulin secretagogues know how to prevent, recognize, and treat hypoglycemic episodes that can occur because of their treatment with insulin — this includes the use of exogenous glucagon to counteract low blood glucose levels.[1]

> **"...the microneedles physically break the outermost layer of skin, and penetrate the epidermis layer below where the dry drug coating is dissolved in the surrounding interstitial fluid."**

Current Practice

The 2013 Canadian clinical practice guidelines on diabetes recommend that a conscious person with severe hypoglycemia should be treated with oral ingestion of 20 g of a carbohydrate, preferably as glucose tablets or an equivalent.[1] The person's blood glucose level should be re-tested in 15 minutes and re-treated with another 15 g of glucose if the blood glucose level remains less than 4.0 mmol/L.[1] For an unconscious person with severe hypoglycemia and no intravenous access, the guidelines recommend treatment with 1 mg glucagon given subcutaneously or intramuscularly, and that caregivers or support persons should call for emergency services.[1] If there is intravenous access, then the preferred treatment is 10 g to 25 g of glucose given intravenously for one to three minutes.[1]

In Canada, exogenous glucagon is indicated for the emergency treatment of severe hypoglycemia in patients treated with insulin when unconsciousness prevents treatment with oral carbohydrates.[6] Currently, glucagon is only available in Canada in powder form, meaning the powder must be reconstituted with the supplied diluent immediately before injection. The recommended dose for adults and children weighing more than 20 kg is 1 mg glucagon administered by subcutaneous, intramuscular, or intravenous injection.[6] A subcutaneous or intramuscular dose of 1 mg glucagon increases mean peak blood glucose levels to approximately 7.5 mmol/L to 7.6 mmol/L within 30 minutes following the injection.[6]

The Evidence

The ZP-Glucagon patch is in early development and only one conference abstract[16] and a clinical trial registration[17] for a phase II study were identified. The study compared the safety and efficacy of two dose levels (0.5 mg and 1.0 mg) of glucagon administered by either the ZP-Glucagon patch or glucagon administered by intramuscular injection (GlucaGen, Novo Nordisk).[16,17] The study was designed as a four-way, open-label, randomized, crossover study in 16 adults with type 1 diabetes who were made mildly hypoglycemic by infusing insulin. The primary outcome was the proportion of patients achieving normal blood glucose levels after 30 minutes. Administration of 0.5 mg or 1.0 mg of glucagon by either the ZP-Glucagon patch or intramuscular injection resulted in normalization of glucose in all study patients. Both patch doses of glucagon had rapid onset of action and the time to response was similar for all four treatment groups.[16]

Safety

According to the conference abstract for the phase II study of the ZP-Glucagon patch, all treatments were well tolerated and no safety issues were reported.[16] No further information on the safety and tolerability of the ZP-Glucagon patch was identified. Given the limited evidence available, potential safety concerns with the patch are yet unknown.

Concurrent Developments

Zosano Pharma is also developing ZP patch transdermal delivery systems for other conditions.[18] A ZP patch product containing zolmitriptan (ZP-Triptan) for migraine therapy is entering phase III trials and another ZP patch product containing parathyroid hormone (ZP-PTH) for use in osteoporosis has completed phase II trials.[12,19,20] A preclinical study that evaluated the feasibility of using the ZP patch system to deliver recombinant human growth hormone (ZP-hGH) has also been published.[11]

Intranasal inhalation is also being investigated as an alternate route of glucagon administration. A recent randomized, crossover, non-inferiority study evaluated the efficacy and safety of a novel intranasal glucagon delivery system (Locemia Solutions, Montreal, Quebec) in comparison with standard intramuscular injection of glucagon for the treatment of insulin-induced hypoglycemia in adults with type 1 diabetes.[21]

Implementation Issues

A more user-friendly delivery system for glucagon than is currently used could potentially reduce the use of emergency services, hospitalization, and product wastage (a consequence of glucagon for injection being improperly mixed).

Product Stability

The preclinical study of the ZP-hGH patch (for recombinant human growth hormone delivery) reported that stability experiments conducted on the patch support that the ZP-hGH patch in the sealed pouch remained stable at 40°C for up to six months with no significant changes.[11] If the ZP-Glucagon patch has a similar stability, this could make it easier for individuals at risk for severe hypoglycemic attacks to carry the ZP-Glucagon patch with them. In comparison, currently available glucagon for injection must be stored at controlled room temperature (15°C to 30°C) before reconstitution, and unused portions must be discarded after reconstitution.[6]

Microneedle Technology

The microneedle technology used in the ZP-patch system could have applicability to a wide range of therapeutic compounds (e.g., small molecules to proteins, peptides, and vaccines) that cannot be administered using currently available transdermal

or oral delivery methods.[9] Potential advantages of microneedle technology compared with injections include reduced pain and bleeding, elimination of needle-stick injuries, potential for controlled drug delivery, ability to self-administer, and acceptance by children and individuals with needle phobia.[7] Possible drawbacks of the technology are delayed onset of action, inability to confirm the dose delivered, most likely a higher cost, and the risk of skin irritation or allergic reactions related to the adhesive patch.[7]

Final remarks

The available evidence for efficacy and safety of the ZP-Glucagon patch is limited as the phase II trial enrolled only a small number of patients and although randomized, the study was designed as an open-label crossover trial. Zosano Pharma had indicated plans to initiate a phase III trial in 2016; however, we found no information on this trial.[14]

As currently available exogenous glucagon requires reconstitution immediately before injection, the ZP-Glucagon patch has the potential to simplify the administration of glucagon and the treatment of severe hypoglycemia. This may be especially beneficial in an emergency situation if the individual is unconscious and caregivers or bystanders are unfamiliar with how to prepare glucagon for injection or how to administer a subcutaneous or intramuscular injection.

Methods — Literature Search Strategy

A limited literature search was conducted using the following bibliographic databases: PubMed, MEDLINE, Embase, and the Cochrane Library. Grey literature was identified by searching relevant sections of the Grey Matters checklist (https://www.cadth.ca/grey-matters). No methodological filters were applied. The search was limited to English-language documents published between January 1, 2012 and January 25, 2017. Conference abstracts published between January 1, 2015 and January 25, 2017 were included in the search results. Regular alerts were used and the search updated until project completion; only citations retrieved before February 10 were incorporated into the analysis.

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